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WO 01/90140 A1

(54) Title: PEPTOIDS AS LIGANDS FOR MELANOCORTIN RECEPTORS

(57) Abstract: A peptoid having binding affinity for a melanocortin receptor, comprises the amino acid sequence AA_4-AA_5-AA_6-DAA_7-NAA_8-NAA_9-AA_{10} wherein AA_4 and AA_5 are each absent or an amino acid; AA_6 is a basic amino acid; DAA_7 is a D-amino acid; NAA_8 and NAA_9 are each N-substituted amino acids; and AA_{10} is absent or an amino acid.

PEPTOIDS AS LIGANDS FOR MELANOCORTIN RECEPTORS

Field of the Invention

This invention relates to peptoids that have binding activity for melanocortin receptors.

Background of the Invention

Melanocortins are peptides originally derived from a larger, precursor protein, i.e. pro-opiomelanocortin. Natural melanocortins share the heptapeptide core sequence Met-Glu-His-Phe-Arg-Trp-Gly. The melanocortins include α-MSH (α-melanocyte-stimulating hormone), β-MSH, γ-MSH, γ-LPH (γ-liprotropin hormone) and ACTH (adrenocorticotropic hormone).

Melanocortins have a wide range of biological activities. They are known to stimulate pigmentation and corticosteroidogenesis, and they have also been shown to induce excessive grooming behaviour in the rat, to stimulate conditioned active avoidance response, to increase blood pressure and heart rate, to accelerate nerve regeneration and to modulate immune responses.

Five neuropeptide receptors for melanocortins have recently been identified and cloned. These receptors have different distribution patterns, both in presence and abundance, over different tissue types. They belong to the family of so-called G-protein-coupled receptors. Melanocortin receptor 1 (MCR-1) is expressed in melanocytes, whereas MCR-2 is the ACTH receptor expressed in, for example, the adrenal gland. Melanocortin receptors 3, 4 and 5 have been found to be expressed in the central nervous system. The cognate ligands of these receptors have profound neuropharmacological effects, such as facilitated arousal, motivation, attention, memory and learning. The ligands have also been implicated in food-motivated behaviour. A relationship with antipyretic activity has also been disclosed.

Many synthetic analogues of melanocortin have been prepared and suggested to have therapeutic utility, by activation or blocking of one or more melanocortin receptors. In general, such analogues lack specificity (selectivity) for the receptors expressed in the nervous system, and/or they lack sufficient binding affinity or capability to induce or block the receptor-mediated response.

Peptides having melanocortin receptor-binding activity, and selectivity for MCR-3, MCR-4 or MCR-5, are described in WO-A-98/27113 and WO-A-99/54358. While active *in vitro*, these compounds are peptides that are unlikely to have sufficiently long half-life in plasma that they can be of therapeutic use.

Various strategies for rendering peptides resistant to breakdown *in vivo* are known. These include the use of D-amino acids and N-substituted amino acids, as in peptoids, but such strategies can severely compromise the specificity and efficacy of the compounds.

Summary of the Invention

According to the present invention, novel peptoids having binding affinity for a melanocortin receptor, and in particular the MC3, MC4 or MC5 receptor, comprise the amino acid sequence

$$AA_4\text{-}AA_5\text{-}AA_6\text{-}DAA_7\text{-}NAA_8\text{-}NAA_9\text{-}AA_{10}$$

wherein AA_4 and AA_5 are each absent or an amino acid;

AA_6 is a basic amino acid;

DAA_7 is a D-amino acid;

NAA_8 and NAA_9 are each N-substituted amino acids; and

AA_{10} is absent or an amino acid.

Surprisingly, it has been found that, provided that NAA_8 and NAA_9, i.e. positions 8 and 9 (referring to the numbering of the amino acids in ACTH), both contain a peptoid building block, a satisfactory degree of potency is retained. In particular, potency is greater than if either position 8 or 9 alone, or position 7, includes a peptoid building block.

Description of the Invention

The term "amino acid" is used herein to describe, not only the 20 naturally occurring amino acids, but also derivatives and peptoid analogues thereof. The skilled man will appreciate that, in accordance with the intention behind this invention, i.e. to minimise loss of activity while increasing half-life, minimum values for each criterion should be retained, e.g. at least as good as for any exemplified compound of the invention. It may be expected that two juxtaposed naturally occurring amino acids will make the compound susceptible to hydrolysis; however, the loss of one or more amino acids from the compound may leave an active structure according to the invention.

In general, the structural characteristics of naturally occurring amino acids will be retained, in terms of the peptide backbone and side-chains, whether in a L-, D- or N-substituted form. Nevertheless, a variety of aromatic residues may be used, e.g. at position 7. F or Cl as a substituent can promote agonist activity; I as a substituent, or

a naphthalene or pentamethylenephenyl residue, can provide enhanced antagonist activity.

The novel compounds are peptoids because the peptide side-chain at positions 8 and 9 at least is on the N atom, rather than the C atom, of the given amino acid in the peptide backbone. Such peptoid (non-chiral) building blocks may also be present at any other position in the compound.

Certain compounds of the invention are preferred. It is preferred that AA_4 (if present) is NNle, Nle or Gly, that AA_5 (if present) is Gly or Asp, that AA_6 is NHis, NLys, His or Lys, that DAA_7 is D-Nal, D-Phe, D-PmP, D-Thi or D-Pyr, that NAA_8 is N-Arg, that NNA_9 is N-Trp or a homologue thereof, that AA_{10} (if present) is Gly or Lys, and/or that the compound is cyclised. In general, each preferred feature confers on the novel compound enhanced potency, half-life and/or selectivity.

Peptoids of this invention typically comprise at least three or four residues (corresponding to positions 6-9).

Peptoids of the invention can be made by standard procedures. The individual amino acids or analogues thereof are known or can be made by known procedures.

By way of explanation, this invention is based on comparison of the properties of a number of peptides/peptoids that have been synthesised; in particular, four peptoids illustrating the invention have been synthesised, using a robotic synthesiser, and are given as SEQ ID NOS:1-4. These were then tested.

The tests, as well as synthetic procedures, are described in WO-A-98/27113. That publication also describes therapeutic indications that may be associated with the characteristics that are found in various tests, and appropriate compositions and dosage regimens. In general, compounds of this invention have longer half-lives, but they may be less potent and therefore require higher dosages in order to obtain the same therapeutic effect.

CLAIMS

1. A peptoid having binding affinity for a melanocortin receptor, which comprises the amino acid sequence

$$AA_4-AA_5-AA_6-DAA_7-NAA_8-NAA_9-AA_{10}$$

wherein AA_4 and AA_5 are each absent or an amino acid;

AA_6 is a basic amino acid;

DAA_7 is a D-amino acid;

NAA_8 and NAA_9 are each N-substituted amino acids; and

AA_{10} is absent or an amino acid.

2. A peptoid according to claim 1, wherein AA_4 (if present) is NNle, Nle or Gly.

3. A peptoid according to claim 1 or claim 2, wherein AA_5 (if present) is Gly or Asp.

4. A peptoid according to any preceding claim, wherein AA_6 is NHis, NLys, His or Lys.

5. A peptoid according to any preceding claim, wherein DAA_7 is D-Nal, D-Phe, D-PmP, D-Thi or D-Pyr.

6. A peptoid according to any preceding claim, wherein NAA_8 is N-Arg.

7. A peptoid according to any preceding claim, wherein NAA_9 is N-Trp or a homologue thereof.

8. A peptoid according to any preceding claim, wherein AA_{10} (if present) is Gly or Lys.

9. A peptoid according to any preceding claim, which is cyclised.

10. A peptoid according to any preceding claim, for use in therapy.

SEQUENCE LISTING

<110> Quadrant Holdings Cambridge Limited

<120> PEPTOIDS

<130> REP06329WO

<140> NOT YET KNOWN
<141> 2001-05-22

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INTERNATIONAL SEARCH REPORT

tn onal Application No
PCT/GB 01/02282

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K7/02 A61K38/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
MEDLINE, CHEM ABS Data, EPO-Internal, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 131, no. 2, 12 July 1999 (1999-07-12) Columbus, Ohio, US; abstract no. 19270, HEIZMANN, G. ET AL: "A combinatorial peptoid library for the identification of novel MSH and GRP/bombesin receptor ligands" XP002177895	1,10
A	abstract & J. RECEPT. SIGNAL TRANSDUCTION RES. (1999), 19(1-4), 449-466 ,	2-9
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 2001	04/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Döpfer, K-P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/02282

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 21571 A (TREGA BIOSCIENCES INC) 6 May 1999 (1999-05-06) page 3, line 1 - line 14 page 4, line 13 -page 17, line 12 claims; examples	1-10
A	WO 98 27113 A (ADAN ROGER ANTONIUS HENDRICUS ;GISPEN WILLEM HENDRIK (NL); BURBACH) 25 June 1998 (1998-06-25) cited in the application the whole document	1-10
A	WO 98 10068 A (UNIV OREGON HEALTH SCIENCES ;FAN WEI (US); LU DONGSI (US); BOSTON) 12 March 1998 (1998-03-12) claims	1-10
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 01/02282

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		CN 1246868 A	08-03-2000
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